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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/874,166	06/04/2001	William Thomas Melvin	12489-003002/UMMC Ref: UM	8129

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/874,166	MELVIN ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-35 and 41-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-35 and 41-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 June 2001* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/043,814.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/01; 9/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comly*.

Notice to Comply	Application No. 09/874,166	Applicant(s) Melvin et al.
	Examiner J. Eric Angell	Art Unit 1635

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other: _

Applicant Must Provide:

☒ An initial or **substitute** computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or **substitute** paper copy of the "Sequence Listing", as well as an amendment directing its entry into the **specification**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
For CRF Submission Help, call (703) 308-4212
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY

DETAILED ACTION

This Action is in response to the communication filed on 4/18/2006.

The communication filed on 4/18/2006 has been entered.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claims 27-35 and 41-44 are currently pending and are examined herein.

Information Disclosure Statement

The information disclosure statements submitted on 6/4/2001 and 9/30/2002 are acknowledged. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Specification/Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Specifically, page 17 of the specification discloses four different nucleic acid sequences which meet the definition set forth in 37 C.F.R. § 1.821, but which have not been assigned proper

sequence identifiers (i.e., they have not been assigned SEQ ID Nos.). Applicants are required to amend the specification to assign SEQ ID Nos. to the indicated nucleotide sequences on page 17 of the specification and to file the items indicated on the attached "Notice to Comply". Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) in response to this Office Action. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g).

Applicant is requested to return a copy of the attached Notice to Comply with the response.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-35 and 41-44 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement for the reasons of record (e.g., see the 10/18/2005 Office Action) which are reiterated below for convenience.

The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

It is noted that claim 27 is drawn to a method for activating T cells in a subject by administering to the subject an amount of a cytochrome P450 CYP1B1 sequence effective to activate T cells that recognize a CYP1B1 epitope. As indicated in the response filed 9/13/04 (see p. 4), "to require that a CYP1B1 sequence (such as a CYP1B1 amino acid sequence or nucleic acid sequence) be administered to the subject..." (Emphasis added). Therefore it is clear that the claim encompasses administering a nucleic acid sequence or an amino acid sequence to the subject.

It is noted that the claims encompass activating T cells in a subject that has cancer (claims 31, 32) wherein the method results in a cell-mediated or humoral immune response against the cancer (claim 33). Since claim 27 is the independent claim it must, by definition, encompass all limitations set forth in the dependent claims. Therefore, claim 27 (as well as all claims dependent on claim 27--i.e., all pending claims) must encompass a method of activating a cell-mediated or humoral immune response against a cancer in a subject. Therefore, all pending claims encompass treating cancer by administering a tumor antigen sequence (either nucleic acid sequence or protein sequence) to a subject having cancer. The claims are not enabled for the reasons set forth in previous Office Actions, which are reiterated below.

The nature of the invention

The claims are drawn to a method of activating T cells in a subject by administering a cytochrome P450 CYP1B1 sequence to the subject in an amount effective to activate T cells that recognize a CYP1B1 epitope, and includes stimulating an immune response against cancer cells. Therefore, the claims encompass cancer immunotherapy (e.g., treating cancer by administering a tumor antigen sequence), also known as cancer vaccination.

The breadth of the claims

The claims are very broad. The broadest claims encompass stimulating T cells in a subject by administering a cytochrome P450 CYP1B1 sequence to the subject in an amount effective to activate T cells that recognize a CYP1B1 epitope. The claims also explicitly encompass administering any CYP1B1 sequence (such as SEQ ID NOS 1 or 2) that activates said human T cells.

The unpredictability of the art and the state of the prior art

The state of the art, including the post-filing art indicates that cancer immunotherapy and gene therapy (which is encompassed by the claims because the claims encompass administering a CYP1B1 nucleic acid sequence) are not methods that can be predictably performed.

For instance, with respect to administering a nucleic acid to a subject (e.g., gene therapy) the relevant art recognizes a number caveats and obstacles that must be overcome before the method can be predictably performed without an undue amount of additional experimentation.

At the time of filing, the relevant art considered gene therapy as a whole to be unpredictable as modes of delivery that would provide efficient expression of genes encoding the therapeutic polypeptide (in this case the immunostimulatory amino acid sequence) sufficient to

result in the desired effect, in this case activating T cells. Currently, the state of the art of gene therapy is still in its infancy as the art is plagued by unpredictability. For instance, Crystal (Science, 1995; 270:404-409) teaches, "All of the human gene transfer studies have been plagued by inconsistent results, the basis of which are unclear", and sites specific examples including inconsistent results, the inconsistency of results in animal models and humans, vector production problems, and vector efficiency (see page 409, columns 1-2). Specifically, regarding the ideal gene therapy vector, Crystal teaches, "The vector should be specific for its target, not recognized by the immune system, stable and easy to reproduce... Finally it would express the gene (or genes) it requires for as long as long as required in an appropriately regulated fashion." (See p. 409, second column).

Verma et al. (Nature, 1997; Vol. 389) teaches, "there is still no single outcome that we can point to as a success story" (see pg. 239, col. 1; Gene Therapy Promises, Problems and Prospects). More recently, Walther and Stein (2000) reaffirms the obstacles to successful gene therapy by stating, "The hurdles to overcome in efficient gene therapy are successful gene transfer of the therapeutic genes, appropriate expression levels associated with sufficient duration of gene expression, and the specificity of gene transfer to achieve therapeutic effects in the patient." (See p. 267, under "Discussion"). Walther and Stein also indicate, "The majority of clinical trials using viral vectors for gene therapy in humans still lack a significant clinical success, defining the still existing barriers to achieving clinical benefits with gene therapy" (See pg.267, Discussion section).

To overcome the teachings in the art (with respect to administering a CYP1B1 nucleic acid sequence), the specification would need to supply direct, correlative guidance on how to

administer the CYP1B1 nucleic acid to a subject in such a way that the nucleic acid is delivered to an appropriate cell such that the nucleic acid expresses the CYP1B1 amino acid sequence in the cell, that the amino acid sequence is properly expressed (e.g., at an appropriate level for an appropriate duration of time and secreted from the cell in an effective amount) such that administration of the sequence effectively activated T cells in the subject such that method resulted in an effective immune response against a cancer in the subject.

With respect to cancer immunotherapy, the relevant art recognizes a number caveats and obstacles that must be overcome before cancer immunotherapy methods can be can be predictably performed without an undue amount of additional experimentation.

For instance, Bodey et al. (2000; previously cited) teaches: "The cancer vaccine approach to therapy is based on the notion that the immune system could possibly mount a rejection strength response against the neoplastically transformed cell conglomerate. However, due to the low immunogenicity of tumor associated antigens, down regulation of MHC molecules, the lack of adequate co-stimulatory molecule expression, secretion of immune inhibitory cytokines, etc., such expectation are rarely fulfilled...faulty antigen presentation which could result in tolerance induction to the antigens contained within the vaccine, and subsequent rapid tumor progression." (Page 2665, column one).

Additionally, Gouttefangeas et al. (2000; previously cited) teaches,

> "As most cancer patients obviously do not mount efficient T cell responses against their tumors, the task is clear: immunotherapies must induce cancer-destroying T cells in patients. Although this goal appears straight forward, effective immunotherapy has remained elusive because of three major problems: first, for many tumors, no or not enough suitable antigens are known; second, no consensus exists for the best antigen

formulation or the route of immunization; and third, tumors under immune attack tend to be selected for antigen loss variants." (See p. 491, first column).

Thus, Gouttefangeas indicates that patients that have tumors which express the tumor antigen do not mount an efficient immune response to these tumors. Therefore, administering a tumor antigen to a patient comprising a tumor that expresses the antigen may not be sufficient to activate an immune response to the human tumor antigen. Furthermore, Gouttefangeas indicates that a single tumor antigen may not be sufficient to activate an effective immune response to the tumor. It is noted that the instant specification has only described epitopes of a single tumor antigen, human CYP1B1. Finally, Gouttefangeas teaches that using immunotherapy for cancer treatment is unpredictable because the treatment can select for tumor cells that do not express the tumor antigen, thus rendering the treatment ineffective in tumors that comprise cancer cells that do not express the antigen.

Furthermore, Radoja et al. (Mol Med 2000; previously cited) teaches that cancer-induced defective cytotoxic T lymphocyte is probably another mechanism how tumor antigen escape immune surveillance. Specifically, Radoja teaches,

> "THE NOTION THAT A DEFICIT IN IMMUNE CELL FUNCTIONS PERMITS TUMOR GROWTH HAS RECEIVED EXPERIMENTAL SUPPORT WITH THE DISCOVERY OF SEVERAL DIFFERENT BIOCHEMICAL DEFECTS IN T LYMPHOCYTES THAT INFILTRATE CANCERS" (abstract). "ACCUMULATION OF CIRCULATING ANTITUMOR IMMUNOGLOBULIN G IN CANCER PATIENTS SHOW THAT THE PRIMING PHASE OF ANTITUMOR IMMUNE RESPONSE IS FUNCTIONAL DURING THE RELATIVELY SLOW PROCESS OF NASCENT TUMOR GROWTH...IN BOTH HUMAN CANCER PATIENTS AND RODENTS BEARING TUMORS OF DIFFERENT HISTOLOGIC ORIGIN, SYSTEMIC IMMUNITY IS NOT PROFOUNDLY SUPPRESSED..." "HOWEVER, INHIBITION OF A SPECIFIC ANTITUMOR IMMUNE RESPONSE HAS BEEN OBSERVED FREQUENTLY. A VARIETY OF MECHANISM HAVE BEEN PROPOSED TO ACCOUNT FOR DEFECTIVE ANTITUMOR IMMUNE RESPONSE, INCLUDING: SECRETION OF SUPPRESSIVE FACTORS IN THE TUMOR MICROENVIRONMENT, THE LACK OF EXPRESSION OF COSTIMULATORY SIGNALS ON TUMOR CELLS, INDUCTION OF REGULATORY T CELLS

> HAVING A SUPPRESSIVE PHENOTYPE, LOSS OF ANTIGEN PRESENTATION FUNCTION IN THE TUMOR, LOSS OF EXPRESSION OF HLA CLASS I ANTIGEN PRESENTING MOLECULES IN TUMORS, TUMOR-INDUCED T-CELL SIGNALING DEFECTS, LOSS OF TUMOR ANTIGEN EXPRESSION, IMMUNOLOGICAL IGNORANCE AND, SINCE MANY TUMOR ANTIGENS ARE EITHER UNMODIFIED SELF OR EPITOPES CLOSELY RELATED TO SELF, THE REDUCTION OF THE REPERTOIRE OF POTENTIAL HIGH AFFINITY ANTITUMOR T-CELL CLONES DURING T-CELL MATURATION IN THE THYMUS" (Introduction).

Thus, it is evident that the skilled artisan, while acknowledging the significant potential of immunotherapy for cancer, still recognizes that such therapy is neither routine nor wholly accepted. Furthermore, significant development and further guidance is necessary for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for the instant methods.

In order to enable the instant claims in light of the state of the relevant art, the applicant must provide guidance/working examples to demonstrate that the CYP1B1 epitopes are highly immunogenic and could provoke a useful immune response without the problems in the cited references or must provide ways to overcome the cited difficulties.

Working Examples and Guidance in the Specification

The specification does not have any working examples that indicate that a CYP1B1 sequence (including a CYP1B1 nucleic acid sequence and a CYP1B1 amino acid sequence comprising SEQ ID NO:1 or SEQ ID NO:2) can be used to: (1) activate T cells in a subject; and/or, (2) stimulate an immune response against a cancer in a subject. The only examples provided indicate that the human CYP1B1 epitopes disclosed (specifically, the amino acid sequences consisting of SEQ ID NO:1 and SEQ ID NO: 2) can be used to raise antibodies against the epitopes in mice. As indicated above activating T cells in a subject and stimulating

an immune response against a cancer using a tumor antigen epitope is not a matter of routine experimentation.

Quantity of Experimentation

Considering the breadth of the claims, and the unpredictability of gene therapy and cancer immunotherapy recognized in the art, additional experimentation is required in order for one of skill in the art to be able to practice the claimed invention. Considering the lack of working examples or guidance in the specification and also considering the teachings of the relevant art that the required experimentation is not routine, the amount of additional experimentation required is deemed to be undue.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability of gene therapy and cancer immunotherapy recognized in the art, the breadth of the claims, the lack of working examples and guidance in the specification, and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed invention is undue.

Response to Arguments

Applicant's arguments on pages 2-9 of the communication filed 4/18/2006 have been fully considered but they are not persuasive.

With respect to the breadth of the claims, Applicants assert that the sequence used in the claimed methods is limited both structurally (it must be a P450 CYP1B1 sequence) and

functionally (it must be a sequence that is effective to activate T cells that recognize a CYP1B1 epitope).

In response, it is acknowledged that the claims limit the sequences to P450 CYP1B1 sequence that is effective to activate T cells that recognize a CYP1B1 epitope. However, even with these limitations, the claims are still very broad. First, the argument that the sequences are structurally limited to "P450 CYP1B1 sequences" does not impart any specific structural limitation at all because the specification does not explicitly define "P450 CYP1B1 sequence". It is also respectfully pointed out that the claims clearly encompass nucleotide and amino acid P450 CYP1B1 sequences. Looking to the specification for guidance, the specification only discloses two specific sequences as CYP1B1 sequences (SEQ ID NO: 1 and SEQ ID NO: 2). Second, there is no guidance provided to indicate which P450 CYP1B1 sequences activate T cells and which do not. In fact, the specification does not even indicate if either of the two disclosed CYP1B1s (SEQ ID NO: 1 and 2) were able to activate T cells.

With respect to the nature of the invention, Applicants assert that the claimed methods generally relate to the use of a tumor associated antigen to activate T cells in a subject. Applicants further indicate that the CYP1B1 sequences can be used to immunize a subject, thereby resulting in activated T cells that recognize a CYPIB 1 epitope and mediate an immune response against a CYP1B1-expressing tumor.

In response, the Examiner does not take issue with Applicant's arguments regarding the nature of the invention. However, the Examine would like to emphasize that the claims encompass treating cancer by administering a tumor antigen sequence cancer immunotherapy,

which is also known as cancer vaccination. Furthermore, it is noted that, based on the nature of the invention, the invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

With respect to the state of the prior art, Applicants refer to U.S. Patent No. 5,589,466 as evidence of the state of the art with respect to the use of nucleic acids to generate an immune response in a subject.

In response, it is respectfully pointed out that each application is examined on its own merits and the circumstances of other applications/patents are not considered in the examination of the instant application. Furthermore, the instant claims are broader than those of the '466 patent because the instant claims encompass administering any P450 CYP1B1 sequence that activates T cells, including nucleotide sequences and amino acid sequences while the claims of '466 patent are drawn to administering non-integrating DNA sequences.

Applicants argue that the gene therapy references (Crystal and Verma) cited in the Office Action do not describe the use of a nucleic acid to induce an immune response against a protein encoded by the administered nucleic acid.

In response, the claims encompass administering nucleic acid sequences that encode a therapeutic amino acid sequence. In the instant case, the claims encompass administering nucleic acid sequences that encode a therapeutic amino acid sequence that is a P450 CYP1B1 amino acid sequence. Furthermore, the cited references teach many of the problems associated

with delivery of nucleic acid sequences that encode therapeutic amino acid sequences such as delivery of the nucleic acid such that it could express the therapeutic peptide sequence in an amount sufficient to have a therapeutic effect, especially in view of the fact the nucleic acid may be recognized by the patient's immune system.

With respect to the cancer immunotherapy articles, Applicants acknowledge that the three references cited describe several obstacles that have been faced in the field. However, Applicants argue, the general obstacles reviewed in those references do not negate the particular experimental findings of the present application that describe the usefulness of CYP1B1 as a target for immunization in cancer patients. Applicants contend that the primary limitation of cancer immunotherapy cited by the Gouttefangeas reference was the lack of suitable antigens for many tumors, which applicants assert is the unmet need that is solved by the present application.

In response, it is respectfully pointed out that applicants have not addressed the problems taught by Bodey and Radoja. Furthermore, it is respectfully pointed out that Gouttefangeas teaches that patients that have tumors which express the administered tumor antigen do not mount an efficient immune response to these tumors. Therefore, administering a tumor antigen to a patient comprising a tumor that expresses the antigen may not be sufficient to activate an immune response to the human tumor antigen. It noted that the instant specification states, "We have now shown that CYPIBI is expressed in a wide variety of malignant tumours of different histogenetic types and is not present in normal tissues..." (see page 18); which indicates that it is likely that the patient's tumor may express the P450 CYP1B1 peptide and thus may not amount an efficient immune response to the tumors. Furthermore, Gouttefangeas indicates that a single

tumor antigen may not be sufficient to activate an effective immune response to the tumor. It is noted that the claims encompass administering a single tumor antigen sequence.

With respect to the relative skill of those in the art, Applicants assert that the level of skill in the biological arts is generally considered to be high.

In response, the Examiner agrees.

With respect to the level of predictability in the art, Applicants again refer to U.S. Patent No. 5,589,466 as evidence of the predictability of the claimed invention.

In response, it is again respectfully pointed out that each application is examined on its own merits and the circumstances of other applications/patents are not considered in the examination of the instant application. Furthermore, the instant claims are broader than those of the '466 patent because the instant claims encompass administering any P450 CYP1B1 sequence that activates T cells, including nucleotide sequences and amino acid sequences while the claims of '466 patent are drawn to administering non-integrating DNA sequences.

With respect to the amount of direction provided by the inventor, Applicants argue that the specification teaches that CYP1B1 sequences can be used to immunize a subject, thereby resulting in activated T cells that recognize a CYPIBI epitope and mediate an immune response against a CYPlBl-expressing tumor and that in view of the knowledge in the art with respect to immunization methods (including nucleic acid immunization as exemplified in the '466 patent), the direction contained in the application as filed was sufficient to permit, at the time the

application was filed, the practice of the claimed methods without undue experimentation and with a reasonable expectation of success.

In response, it is acknowledged that the specification indicates that CYP1B1 sequences can be administered to a subject in order to mediate an immune response against a tumor that expresses the CYP1B1 peptide. However, the cited prior art teaches that, at the time of filing, cancer immunotherapy was an unpredictable method of treatment for cancer. Furthermore, the specification does not disclose how to overcome the problems recognized in the prior art. Additionally, with respect to the '466 patent each application is examined on its own merits and the circumstances of other applications/patents are not considered in the examination of the instant application.

With respect to the existence of working examples, Applicants argue that they need not have actually reduced the invention to practice prior to filing a patent application and that the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without undue experimentation. Applicants argue that the specification discloses experimental findings clearly showing that CYP1B1 is expressed in many types of cancers, but not expressed in those normal tissues studied, and therefore the person of ordinary skill in the art at the time of filing of the present application would have reasonably expected that CYP1B1 sequences could be used to generate an immune response against CYPlBl-expressing tumor cells.

In response, it is acknowledged that working examples demonstrating reduction to practice is not generally required. However, the specification must disclose how to overcome the

problems taught the prior art which render the claimed invention unpredictable. In the instant case, the specification does not demonstrate how to overcome the obstacles taught in the prior art. Furthermore, considering the state of the art at the time of filing (as evidenced the prior art cited in the rejection), one of skill in the art, at the time of filing, would not have reasonably expected that CYP1B1 sequences could be used to generate an immune response against CYPlBl-expressing tumor cells without performing an undue amount of additional experimentation.

With respect to the quantity of experimentation required to practice the claimed invention, Applicants argue that a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Applicants contend that based on the instant disclosure only routine preparation and experimentation would be required for the person of ordinary skill to use such sequences to induce an immune response in a subject.

In response, in view of the teaching of the prior art, the amount of additionally experimentation would not be routine. The additional experimentation would amount to trial and error experimentation and would constitute an inventive step(s) over the prior art.

With respect to the Gribben article (submitted by Applicants with the 5/31/2005 response), Applicants argue that Gribben was not cited to establish the state of the art at the time of filing. Instead, it was provided as a demonstration that CYPIBI sequences can be used

effectively to stimulate an anti-CYPlBl immune response and provide a clinical benefit to cancer patients.

In response it is acknowledged that Gribben was not cited establish that state of the prior art at the time of filing. However, contrary to Applicants assertion, Gribben does not demonstrate that CYP1B1 sequences can be used *predictably* to stimulate an anti-CYPlBl immune response and provide a clinical benefit to cancer patients. As previously indicated, Gribben teaches that the CYP1B1 sequences were administered to 18 patients and 6 of these patients developed "immunity" to CYP1B1 (e.g., see abstract). Therefore, 12 of the 18 patients did not develop immunity. Furthermore 5 of the 6 patients which developed "immunity" required further salvage treatment for progressive metastatic disease (e.g., see abstract). Gribben teaches that it is not clear why 12 of the patients did not develop immunity and why additional salvage treatment was required in 5 of the 6 patient which developed CYP1B1 immunity (e.g., see pages 5-7). Furthermore, Gribben teaches,

> "Whether the mechanism of response is immunologically mediated or whether the generation of anti-CYP1B1 immunity has biologically altered tumor cell resistance or the microenvironment, we believe that these results are of considerable interest and should be verified and further explored. We, therefore, present these data as a hypothesis to be addressed in ongoing and future tumor vaccine studies. Such studies should determine not only which patients develop immunity but also whether patients who develop immunity can be given additional therapy, including conventional antitumor drugs or agents that either enhance immunity or reverse immune suppression to induce clinically beneficial responses." (See page 7, second column)

Therefore, even in light of the teaching of Gribben, the use of CYB1B1 sequences to stimulate an effective T-cell response against cancer cells is, at best, unpredictable and further experimentation is required.

Applicants assert that even though Gribben did not describe a positive outcome in every patient to which a CYPIBI sequence was administered, a compound undoubtedly need not be effective in every patient in order to have clinical utility.

In response, it is acknowledged that a positive result in every patient is not required. However, the fact that 12 of the 18 patients (i.e., 2 out of every 3) did not develop immunity (and it is not known why) is evidence that the claimed method is not predictable.

Applicants also argue that the passage cited in the previous Office Action was out of context because it is in the first paragraph of the introduction of Gribben and Gribben later concludes a review of the literature by stating the data suggests that CYP1B1 can function as a nearly universal tumor antigen and supported investigation of CYP1B1-directed vaccination for the treatment of human cancer.

In response, it is noted that Gribben appears to be reviewing articles that were published after the instant application was filed. Therefore, Gribben's review of the literature is not a review of the state of the art at the time of filing. Furthermore, Gribben supporting investigation of CYP1B1-directed vaccination for the treatment of human cancer demonstrates that the method is not predictable because otherwise further investigation would not be required.

With respect to the assertion that Gribben relies on critical features that were not disclosed in the specification nor taught in the prior art, including the use of an inactivated CYP1B1 DNA formulated within biodegradable poly-DL-lactide-coglycolide microparticles, Applicants argue that there is no evidence of record to suggest that these particular features are critical and that other CYP1B1 sequences (e.g., wild type CYPIBI) and other means of

delivering DNA (e.g., administration of naked DNA) could not also be used to induce an immune response in a subject.

In response, in view of the prior art teaching that delivery of the nucleic acid sequence which encodes the therapeutic peptide is critical (e.g., see Crystal, Verma and Walther, as indicated above), the formulation that was used to deliver the nucleic acid is deemed to be critical. Furthermore, Gribben appears to use a pool of inactivated CYP1B1 peptides (e.g., see page 2 under "Immunologic monitoring"). The instant specification and prior art do not recognize any "inactivated" CYP1B1. The fact that Gribben used the particular formulation and "inactivated" CYP1B1 peptides indicates that Gribben advanced the state art beyond what it was at the time of filing.

Therefore, in view of the Wands factors *as a whole,* the specification does not provide an enabling disclosure for the claimed invention because an undue amount of additional experimentation would be required in order for one of skill in the art to be able to predictably practice the claimed invention to its full scope.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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